Virtual Reality for Amplified Musculoskeletal Pain Syndrome in Adolescents: A Pilot Randomized Controlled Trial

MS Thesis Proposal

Saumya Vinod Joshi, MD

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Committee Chair: Raveendhara R. Bannuru, MD, PhD
Statistical Mentor: Lori Lyn Price, MAS, MLA
Project Mentors: Trevor E. Davis, MD; Yujuan Zhang, MD
External Advisers: Chenchen Wang, MD, MSc; Laurie C. Miller, MD; Caitlin M. Neri, MD, MPH

INTRODUCTION:

About one in every four adolescents experiences chronic pain [1], which is defined as recurrent or persistent pain for more than three months [2]. Amplified Musculoskeletal Pain Syndrome (AMPS) is a pain syndrome with excessive musculoskeletal pain without a primary organic etiology. This includes Complex Regional Pain Syndrome (CRPS), as well as localized and diffuse amplified musculoskeletal pain syndromes, the latter also referred to as Juvenile Fibromyalgia Syndrome (JFS). The prevalence of AMPS in the pediatric age group is as high as 7.5% [3]. While these adolescents suffer from chronic pain, they also have higher rates of depression [3, 4] lower quality of life and greater school absenteeism [4]. Moreover, the caregivers of these adolescents suffer considerable financial, social, and psychological consequences [1] [5].

The current multimodal approach to the treatment of AMPS includes cognitive behavioral therapy, and aerobic and neuromuscular exercise which while useful, is very time and labor intensive. Implementation of these multicomponent treatment regimens is difficult to coordinate, expensive, not fully reimbursed by insurance companies, and poorly complied with by many families [6-8]. Therefore, investigation of alternative strategies for the management of these adolescents remain needed.

A potential strategy is to assess the role of Virtual Reality (VR) as a treatment modality for these patients. Virtual Reality is a state-of-the-art technology that consists of elements including a computer-generated virtual world, immersion, sensory feedback and interactivity [9]. In the past two decades VR has established itself as a very effective, safe and well-accepted form of distraction for acute painful procedures for adults and children alike, including patients receiving burn care, intravenous placements and dental procedures [10]. In adult patients, VR technology has also been successfully applied for chronic pain conditions such as neuropathic pain [11], phantom limb pain [12], complex regional pain syndrome [13, 14], chronic neck pain [15, 16] and

fibromyalgia patients [17-26]. However, to date there are no studies that have evaluated the use of VR for chronic pain syndromes in the pediatric population.

If VR is shown to reduce pain in adolescents with AMPS, the implications could be far-reaching. It might provide transient analgesia during the initiation of typically painful desensitization physical therapy. It can help avoid potentially harmful polypharmacy including the use of opioids in emergency rooms and provide another treatment option for non-responders to standard of care. Finally, AMPS patients can be more successful in self managing their pain in their home environment with the use of VR.

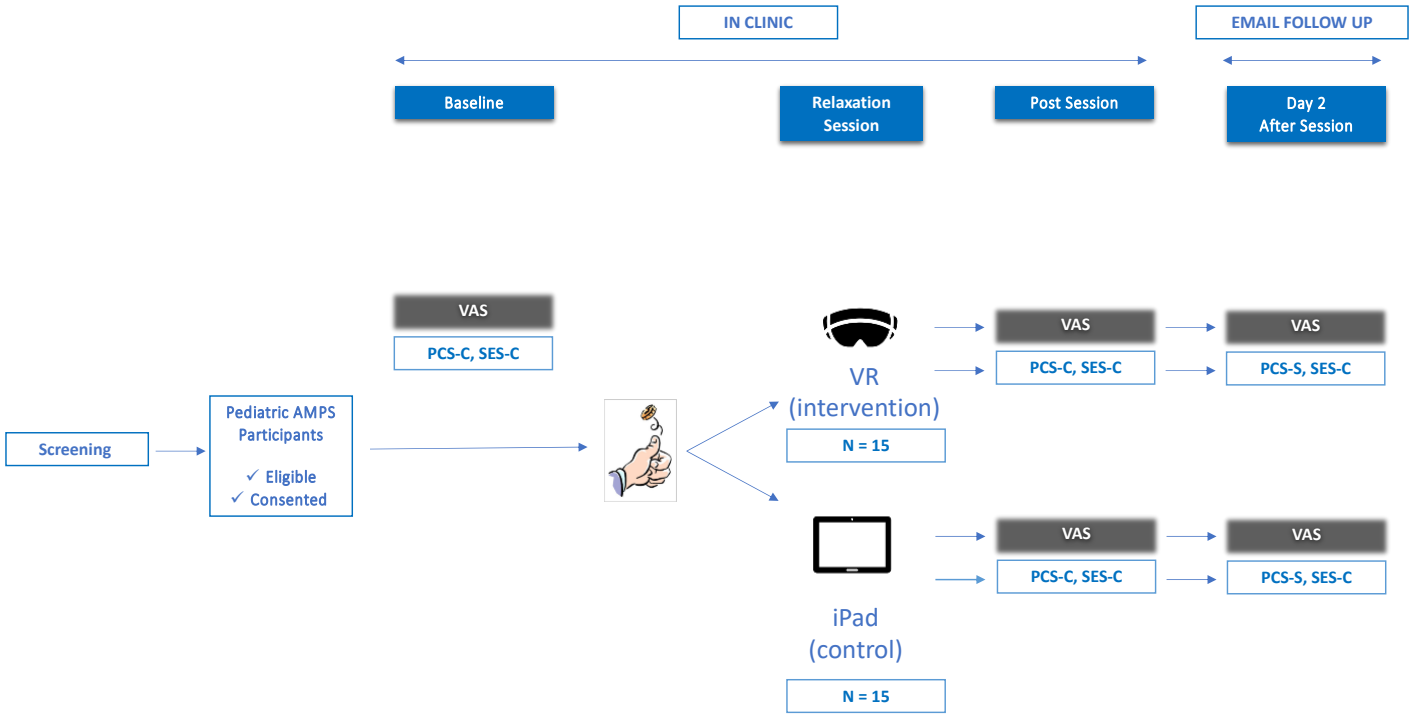
The primary aim of this pilot study is to assess the feasibility and acceptability of VR for adolescents with AMPS. A secondary aim of this study is to calculate measures of change in pain and their variability.

METHODS:

Study Design:

The proposed study is an unblinded pilot randomized controlled trial to assess feasibility and acceptability of VR. Participants will be randomized to either VR or a control arm. The application used for the VR session is "*Happy Place*" [27], which will be delivered via a stand-alone head mounted device, Oculus GO [28]. The participants in the control group will watch the same application on a non-immersive modality, the iPad (Apple Inc. Cupertino CA) for the same duration. In both arms, the intervention will last 10 minutes. Measurements of pain intensity (Visual Analogue Scale or VAS [29]), pain catastrophizing (PCS-C [30] and self-efficacy to manage pain (SES-C [31]) will be collected immediately prior to the session, immediately after the session, and 2 days after the session (Figure 1).

Figure 1.



Inclusion Criteria:

1. Age between 13 years and 17 years old (inclusive) at the time of consent (younger children's heads will likely be too small to use the VR headset [32] and 17 is the upper age limit for the definition of pediatric population).
2. A diagnosis of AMPS, including CRPS, or localized or diffuse amplified pain syndrome as determined by the primary pediatric rheumatologist and coded in EMR.
3. Informed consent for caregivers and child assent for participants.

Exclusion Criteria:

1. An underlying organic cause that can explain the pain including inflammatory, infectious, traumatic or malignant etiologies as determined by the primary pediatric rheumatologist.

2. Participant or caregiver report of any history of motion sickness, underlying epilepsy, severe headaches in the participant or other conditions where the use of visual exposures to stimuli is contraindicated.
3. Inability to report a pain score and/or incapacity to give assent due to intellectual deficit.
4. Blindness.
5. Participants who do not speak English will be excluded due to the unavailability of the content of the VR application used in this study in languages other than English.
6. Any other condition that the investigators think can compromise the integrity of the study or subject safety.

Participant Selection and Recruitment Plan:

Participants will be recruited from the adolescent AMPS population receiving care at Tufts Medical Center, Boston, MA and affiliates. Participants will be identified through clinic interactions and EMR ICD searches at the pediatric rheumatology clinic in Boston and the Tufts affiliated pediatric rheumatology satellite clinics in Massachusetts including Woburn, Lawrence, Brockton and Chelmsford. The setting of the interventions will be in a private clinic room at one of the sites.

Assessments:

This will include collecting data on participant age, gender, date of birth, race, ethnicity, and date of study visit. The type of AMPS (CRPS, localized AMPS or diffuse AMPS), painful areas of the body, duration of onset of AMPS symptoms and time since AMPS diagnosis will recorded. Participants will be asked if they have been taking any medications, counseling or therapy for anxiety, depression or mood disorder in the last six months. A list of active medications and whether the study interventions took place as a part of a regular clinic visit or a separate study visit will be reported. VAS, PCS-C and SES-C will be collected at baseline, immediately after intervention and two days post-intervention.

Randomization and Allocation Concealment:

A stratified block randomization with an equal allocation ratio of 1:1 for the intervention and control groups will be used. The participants will be randomly allocated to VR (intervention group) or iPad (control group) using a computer-generated random number sequence constructed by a biostatistician (LLP). The randomization will be stratified on the baseline pain score (VAS<40 and VAS≥40). This is to attempt to distribute pain scores evenly across the randomization groups.

VR (Intervention Group):

VR application *Happy Place* (© Mimerse) will be used as the intervention. It will be relayed through Oculus GO, which is a head mounted VR device with earphones. *Happy Place* is a publicly available application for pain and incorporates the critical elements of VR, namely immersion and interactivity. The scene is a serene lakeside campground with guided relaxation and soothing music. Approximately 50 'gaze objects' are placed around a scene and gazing at them triggers an event (e.g. gazing at the radio will play a song). The entire duration of the experience will be 10 minutes. It is based on previous studies using immersive VR for chronic pain in the adult population [24, 33] and the mean duration of use of *Happy Place* in the chronic pain population reported by the developers.

iPad (Control Group):

The participants in the control group will watch the flat version of *Happy Place* on an iPad (Apple Inc. Cupertino CA) with headphones. It will deliver the same content for the same duration but will differ from the intervention group in two ways: first, lack of an immersive environment, and second, lack of interactivity with the environment. This will allow the comparison of the effects of immersion and interactivity inherent to VR in the two groups.

Outcome Measures:

Feasibility and Acceptability:

Reporting feasibility (delivery) and acceptability (uptake) of VR in adolescents with AMPS is the primary aim of this pilot trial. Primary outcome for the feasibility will be recruitment rate, which is defined as the proportion of screened patients who consent for the trial within the study period. As a secondary outcome of feasibility, participant response will be measured, which will be assessed by estimating the completion rate of outcome measure questionnaires on day 2 after the study visit in the two groups.

A questionnaire will be administered to both participants and caregivers immediately after the study session to assess the acceptability of the intervention and control modalities. Questions will access prior use of VR, iPad and *Happy Place (simply yes/no variables)*. The degree of immersion and fun experienced during the interventions will be measured on a 0-100 scale, with higher scores representing more immersion and fun. In addition, side effects (dizziness, nausea, and headache) experienced during the interventions will also be reported on a 0-100 scale. Open-ended questions will assess the preferences of participants about their VR or iPad experience, their suggestions for improvement, and willingness to try it in the future.

The pain measures collected in this study will be: pain intensity reported on a Visual Analog Scale (VAS) [29], pain catastrophizing reported on Pain Catastrophizing Scale - Children (PCS-C) [30]; and self-efficacy to manage pain reported on Self-Efficacy Scale for Child Functioning (SES-C) [31].

Visual Analog Scale (VAS): It is a straight horizontal line; usually 0 mm to 100 mm where 0 denotes ‘no pain’ and 100 denotes ‘pain as bad as it could possibly be’. The participant marks a point on the line that they feel represents the perception of their current pain. The VAS score is then determined by measuring in millimeters

from the left-hand end of the line to the point that the participant marks. In this study REDCap's functionality to mimic the VAS using a sliding scale of 0 (labeled "no pain") to 100 (labeled "pain as bad as it could possibly be") will be employed.

Pain Catastrophizing Scale-Children (PCS-C): The PCS-C [30] is an adaptation of the Pain Catastrophizing Scale [34] with established construct and predictive validity in 8-16-year-old participants [30, 35, 36]. It is a self-report measure which includes 13 items about the thoughts and feelings experienced when a child is in pain. Respondents use a 5-point rating scale (where 0 = never to 4 = always), to indicate how often they experience each thought or feeling. Possible scores range from 0-52. Higher score represents worse outcome.

Self-Efficacy Scale for Child Functioning (SES-C): The SES-C is a reliable and validated self-efficacy measure for children 9–18 years of age with chronic pain. The child version has established psychometric properties, excellent reliability and strong evidence for construct validity [31]. It consists of 7 Likert scale questions with a range from very sure (=1) to very unsure (=5). Scores range from 7 to 35, with lower scores reflecting greater self-efficacy to manage pain.

Sample Size Calculation:

We aim to recruit a total of 30 participants with 15 participants in each arm. This is based on the estimate of how many participants the investigators can practically enroll within the timeframe of this study (8 months). The pediatric rheumatology clinic at Tufts Medical Center saw 55 new referrals for adolescents with AMPS in the past year (January 2018 – December 2018): which is 4-5 new patients per month. At this rate, we will have access to about 35 (32-40) new AMPS patients (as the recruitment period will run for 8 months: January 2019 to August 2019). In addition, we will screen participants from the pool of established patients from the past year (n=55). Thus approximately 90 AMPS patients will be available for screening.

A sample of 30 is feasible to recruit as we estimate that around 30% of the total screened patients (90) will be eligible and consent to the study. This is based upon the patient demographic in our clinic. Many chronic pain patients are younger than 13 years or older than 17 years or have an underlying disease to explain the pain; both of which are exclusion criteria. However, this proportion is very tentative and based on incomplete data, which the pilot trial will help address.

Our primary feasibility outcome is recruitment rate defined as proportion of screened patients who will consent to the trial within the study period. If the recruitment rate is 30%, the 95% CI will range from 15% to 49% with a width of 34%. The recruitment potential is an important outcome because we are planning for a subsequent hypothesis-testing RCT of the efficacy of VR for AMPS in adolescents. If the recruitment rate is less than 30% it might take too long to run the future trial.

Data Management Plan:

Participants will enter their own data using the Research Electronic Data Capture (REDCap) software. On submission of the questionnaires, the data will be sent and securely saved in REDCap. Data will be exported from the REDCap database into R Studio for analysis. Consent / assent forms will be stored in a locked cabinet in a locked office.

Data Analysis Plan:

Numbers identified as potentially eligible, approached, and recruited during the course of the trial will be reported descriptively. For each group, losses and exclusions after randomization if any, together with reasons (e.g., participant's unwillingness to use iPad) and numbers analyzed will be reported. The baseline

demographics and clinical characteristics of the two groups will be reported including type, site of AMPS, duration of AMPS symptoms, time since diagnosis, active medications, psychological co-morbidities etc.

Feasibility outcomes will be described using percentages. These will include the primary outcome of recruitment rate defined as proportion of screened patients who consented to the trial within the study period. Completion rate of the online survey at day 2 after the study will also be calculated.

Means and percentages will be used to reports the results of questions assessing acceptability, including the immersion and fun scores, as well as adverse events. The preferences of participants about their VR or iPad experience, their suggestions for improvement and willingness to try it in the future will be reported narratively. Any technical difficulties encountered with the VR and iPad devices will also be reported.

The mean baseline pain measures, as well as change from baseline, will be reported along with their standard deviations.

Human Subject Protection:

Ethical approval for this trial was obtained on 12/03/2018 from the Institutional Board Review of Tufts Medical Center, Boston. A written child assent and informed consent will be obtained from all eligible participants and their caregivers respectively before participating in the study.

Figure 2: Timeline

	# Months					
Project Milestones	**3**	**2**	**3**	**8**	**3**	**2**
Literature Review & Study Conceptualization	**Apr 2018 - Jun 2018**					
Development of Pilot RCT Protocol		**Jul 2018 - Aug 2018**				
IRB Approval			**Sept 2018 - Nov 2018***			
Recruitment and Data Collection				**Jan 2019 - Aug 2019**		
Data Analysis and Manuscript Writing					**Sept 2019 - Nov 2019**	
Thesis Submission						**Dec 2019 - Jan 2020**

(*approved 12/03/18)

Stakeholder Engagement Plan:

The key stakeholders in this study are adolescents with AMPS and their families. Potential stakeholders include health care professionals working with these patients including but not limited to primary care pediatricians, pediatric rheumatologists, orthopods, emergency room physicians, and providers at pediatric pain clinics. In

addition, VR devices and application developers, child health advocates and insurance providers are stakeholders.

It is imperative for the success of VR as an intervention for AMPS that it is based on and informed by the values and preferences of the adolescents intended to use it. An important objective of this study, therefore, is to obtain acceptability measures from the participants and their families via a REDCap questionnaire. Qualitative data generated in this study will inform future research tailored to adolescents with AMPS using VR. In addition to participants, their parents will also be engaged in providing feedback regarding their experience with the relaxation session. The vast majority of participants recruited in this trial are likely to be female and white, consistent with the TMC pediatric AMPS population. Future larger studies can attempt to recruit a sample more representative of different gender/ethnic groups.

The director of the Center of Complementary and Integrative Medicine at Tufts Medical Center and the director of a pediatric pain clinic from another tertiary care hospital in Boston have been consulted from the design phase of this trial. Finally, the CEO of Mimerse, the company who build the application used as the intervention in this trial (*Happy Place*) was also consulted for technical feedback in the design phase. They will be updated and consulted every 6 months throughout the course of this study for their feedback.

Strengths and Limitations:

The proposed pilot trial is the first study to examine immersive VR as a novel non-pharmacologic intervention for adolescents with AMPS and also in any chronic pediatric pain population. It is designed to report the feasibility and acceptability of a randomized clinical trial using immersive VR in the adolescent AMPS population as a transient analgesic modality. It explores alternative mechanisms of action of VR, other than distraction, by measuring cognitive pain scores including PCS-C and SES-C. Finally, it explores the inherent

effect of 'immersion' created by the VR technology by using the same content for the same duration delivered via VR in intervention arm and a flat screen in the control arm.

This trial has potential limitations, the biggest being the choice of the content *(Happy Place)* based on availability and not the values and preferences of adolescents with chronic pain. In addition, the participants, intervention administrator, and data analyzer are all unblinded to the groups. Although the participants in the VR group do not know what intervention the control group is receiving, they are likely to experience a novelty effect with the use of the immersive VR device. This is unlikely to happen with the participants using the iPad and represents a potential bias. Although the primary outcome is self-reported pain score, which is accepted as the best measure of pain, it still remains a subjective outcome. Finally, VR naive and non-naive patients are both likely to be included in the trial.

Conclusion:

This pilot trial will be the first study to report the feasibility and acceptability of immersive VR as a potential non-pharmacologic treatment for adolescents with AMPS. Its primary outcome, recruitment rate will help inform the feasibility of a future definitive randomized controlled trial. It will assess the acceptability of using both the immersive VR via the headset and the non-immersive VR via the iPad. If adolescents with AMPS find success using VR, it may have the potential to become a major advance in pain management. Finally, the use of VR could also reduce health care costs and lead to an expanded use in other settings, such as emergency rooms.

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